Original Article

Pediatric urothelial cancer: a cross-sectional descriptive analysis of the National Cancer Database

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Background: Urothelial cancer is a rare pediatric malignancy; previous analyses suggest lower rates of recurrence and death as compared to adults. We analyzed pediatric bladder cancer information in a national database, hypothesizing that survival would be better in children than adults.

Methods: We analyzed the 2004–2016 National Cancer Database (NCDB) for children and adolescents (0–18 years) with urothelial bladder cancer. Rhabdomyosarcoma patients were excluded. Assessed variables included TNM staging, pathology, tumor size, surgical procedures, and post-operative re-admissions. Overall survival was defined as months since diagnosis as of last follow-up.

Results: Of 140 urothelial tumors reported to NCDB between 2004–2016, 75.7% (N=106) were stage 0 at diagnosis, 6.4% (N=9) were stage I, 2.9% (N=4) were stage II and 3.6% (N=5) were stage IV, while 11.4% cases (N=16) were unknown. From available mortality data (121 patients), no patients died after definitive surgical resection. Only 1 mortality was reported at 90 days, although cause of death was reportedly unknown. Three (2.5%) patients were lost to follow-up, and most (96.7%) were alive at 90 days.

Conclusions: Short-term survival outcomes among children and adolescents with urothelial bladder tumors captured in NCDB are reassuring. Future investigations focused on long-term outcomes and appropriate surveillance in this rare patient cohort are imperative to better guide management options.

Keywords: Bladder cancer; pediatric; urothelial cancer; papillary urothelial neoplasm of low malignant potential (PUNLMP); survival

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Introduction

Urothelial cancer is a rare pediatric malignancy. Previous analyses (most relatively small case series) suggest a low rate of recurrence and death compared to adults (1,2). Given the rarity of this malignancy in children and the lack of robust outcome data, there is some controversy in the optimal surveillance strategy. Traditionally, most authors have argued for a surveillance protocol closely resembling typical adult protocols (3), while others argue for a less invasive approach (4,5).

Prior studies have examined the epidemiology and outcomes in pediatric bladder malignancies. Alanee *et al.* performed an analysis of the Surveillance, Epidemiology, and End Results (SEER) database and found that rhabdomyosarcoma and papillary urothelial neoplasm of low

malignant potential (PUNLMP) were the most common tumors in children (1). While they noted excellent 5-year survival rate of 97.3%, the study was limited by both a lack of clarity on PUNLMP inclusion (SEER documentation suggests that this diagnosis is not typically included in that database) and by their inclusion of rhabdomyosarcoma, for which well-established treatment and surveillance protocols already exist (6). In a systematic review of the literature, Rezaee *et al.* similarly found very favorable outcomes with a 10.7% rate of disease recurrence or death (2). While methodologically appropriate, this study did not report outcomes based on tumor histology, stage, or surveillance protocol.

Given the paucity of high-quality literature on the outcomes of pediatric urothelial cancer, we sought to examine a robust data source, the National Cancer Database (NCDB). We hypothesized that pediatric urothelial neoplasms have favorable outcomes with few local or distant recurrences compared to adults, and thus may benefit from further investigation to guide less-invasive surveillance protocols. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-419/rc).

Methods

Data source

The 2004–2016 NCDB includes deidentified data on patients diagnosed and treated at cancer institutions throughout the United States. It contains data from more than 1,500 institutions and includes roughly 70% of all newly diagnosed cancer cases. Because NCDB is a de-identified database, consent was not obtained. This study was deemed exempt from human studies research review by our Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Cohort

We included pediatric patients (0–18 years of age) with a diagnosis of bladder (urothelial) cancer. Rhabdomyosarcoma patients were excluded. Abstracted variables included TNM staging, pathology, tumor size, surgical procedures, and post-operative re-admission(s). Race/ethnicity categories were converted to US Census reporting categories. Tumor staging was reported per American Joint Committee on Cancer (AJCC) TNM staging categories. The primary outcome was overall survival, measured in months since diagnosis. Within NCDB, vital status of patients is recorded as the date of initial diagnosis to date of last contact or death.

Statistical analyses

Descriptive statistics were analyzed for demographics, histology, and staging. Categorical variables were presented as frequencies with percentages and continuous variables as means with standard deviations or medians with interquartile range (IQR) depending on the distributions. SAS and Microsoft Excel were used for statistical analysis. Although we had initially planned to perform survival analyses with formal hypothesis testing (e.g., Kaplan-Meier plots, log-rank tests, etc.), the number of mortality events was significantly lower than anticipated. Thus, only descriptive statistics were reported.

Results

Cohort characteristics

A total of 275 patients who had pediatric bladder cancer diagnosed between 2004–2016 were identified. Of these, 135 rhabdomyosarcoma patients were excluded. The remaining 140 records were individually reviewed to ensure that they exclusively contained patients with urothelial cancer (predominantly PUNLMP). This cohort also

Highlight box

Key findings

- Short term outcomes for pediatric patients with urothelial bladder tumors are generally reassuring.

What is known and what is new?

- Urothelial bladder tumors are a rare malignancy in pediatric populations and as such there is a paucity of data on long term outcomes, disease recurrence and surveillance modalities.
- This manuscript highlights the importance and need for long term data in these patients by analyzing a large, centralized national database.

What is the implication, and what should change now?

- Pediatric bladder tumors require further investigation to evaluate whether invasive adult protocols are truly the most effective monitoring strategy in a cohort with positive overall survival and disease-free recurrence rates.

Table 1 Demographics and population characteristics of study cohort

Characteristic	Values (N=140)
Age, years, median (IQR)	15.8 (12.3–19.3)
Gender, n (%)	
Male	86 (61.4)
Female	54 (38.6)
Race, n (%)	
White	117 (83.6)
Black of African American	9 (6.4)
Asian	6 (4.3)
Other	3 (2.1)
Unknown	5 (3.6)
Ethnicity, n (%)	
Not Hispanic or Latino	111 (79.3)
Hispanic or Latino	19 (13.6)
Unknown	10 (7.1)
Insurance status, n (%)	
Not insured	6 (4.3)
Private insurance	89 (63.6)
Medicaid	29 (20.7)
Medicare	9 (6.4)
Other government	3 (2.1)
Unknown	4 (2.9)
Income quartile, n (%)	
<$38,000	24 (17.1)
$38,000–$47,999	26 (18.6)
$48,000–$62,999	37 (26.4)
≥$63,000	53 (37.9)
Geographic area, n (%)	
Metro	117 (83.6)
Urban	20 (14.3)
Rural	1 (0.7)
Unknown	2 (1.4)

IQR, interquartile range.

included patients identified as having urothelial papilloma, transitional cell carcinoma, micropapillary transitional cell carcinoma, atypical adenoma and papillary adenoma. Demographic and clinical details are summarized in *Table 1*.

The median age at diagnosis was 15.8 years old. Most were male (61.4%) and White (79.3%); 13.6% were identified as Hispanic or Latino. Overall, most were impressively free of medical comorbidities: 93.6% scored a 0 on the Charlson-Deyo comorbidity index (7). Of the nine patients with identified comorbidities, five had a score of 1, three scored 2, and one had a score of 3 (i.e., moderate comorbidity).

Socioeconomic and geographic factors

At the time of initial diagnosis/treatment, almost two thirds of patients (63.6%) had private insurance/managed care while the next largest group—20.7%—had Medicaid. Median annual income for a plurality of families was at least $63,000. Most patients lived in metropolitan areas (83.6%).

Diagnostic and staging results

Of the tumors in this cohort, 82.1% (N=115) were categorized as *in situ*/carcinoma *in situ* and only 17.9% (N=25) were considered invasive; 67.1% (N=94) were variably recorded as well differentiated, moderately differentiated, moderately well differentiated, or intermediate differentiation. Only 5% (N=7) were categorized as poorly differentiated, while an additional 5% (N=7) was categorized as undifferentiated, anaplastic. The remaining 22.9% of the observed data (N=32) was graded as cell type not determined, not stated or not applicable, unknown, or high-grade dysplasia.

Of the 140 cases reported between 2004–2016, 75.7% (N=106) were stage 0 at time of diagnosis, 6.4% (N=9) were stage I, 2.9% (N=4) were stage II and 3.6% (N=5) were stage IV while 11.4% of cases (N=16) AJCC staging was unknown.

Tumor characteristics

A total of 119 (85.0%) patients were classified as having a papillary urothelial carcinoma or PUNLMP. The next largest histologic group in this cohort was comprised of urothelial papilloma or transitional cell carcinoma which accounted for 17 cases (12.1%). The remaining 4 cases were histologically classified as papilloma, micropapillary transitional cell carcinoma, atypical adenoma, and papillary adenoma.

Table 2 30- and 90-day mortality outcomes

Variables	Values (n=140), n (%)
30-day mortality	
Alive	119 (98.3)
Alive (<30 days of contact, or last contact date missing)	2 (1.7)
Dead	0
Missing	19 (not counted in %)
90-day mortality	
Alive	117 (96.7)
Alive (<90 days of contact, or last contact date missing)	3 (2.5)
Dead	1 (0.8)
Missing	19 (not counted in %)

Intervention data

Intervention data within NCDB is divided into diagnostic and surgical categories. Regarding diagnostics, 125 (89.3%) of the 140 patients records indicate that no diagnostic or staging procedure was performed as part of the initial diagnosis and work up. A biopsy was performed at the primary site in 13 patients (9.3%) as part of the initial diagnosis. One (0.7%) patient underwent surgical exploration at which time the patient was not recorded as biopsied or treated; an additional 1 (0.7%) patient had incomplete data.

In 95.7% (N=134) of the patients, surgery of the primary site was performed. Of the available data (6 missing), 87.3% (N=117) of patients underwent a surgical procedure at time of initial diagnosis and 81.3% (N=109) of patients underwent "definitive surgery" at the primary site at the time of initial diagnosis; an additional 25 (18.7%) underwent definitive surgery of the primary site at a later date.

Primary surgical technique is unknown or missing in 63 patients. Of the remaining 77 patients, most (81.8%) underwent endoscopic intervention. Surprisingly, 9.1% of these patients reportedly did not undergo surgery of the primary site, and 9.1% of these patients underwent open surgery or an unspecified surgical approach. Following surgical intervention, only 1 (0.71%) case was reported to have macroscopic residual tumor present following resection. In 55 (39.3%) cases, all margins were grossly and microscopically negative. Fifty-nine (42.1%) cases did not have evaluable margins or were indeterminate.

Most patients (78.3%) were discharged home the same day; only 5 (3.6%) had an unplanned readmission within 30 days of discharge following their initial surgery.

Mortality outcomes

Of available mortality data (121 of 140 patient records, *Table 2*), no patients died within 30 days from the date of the first (or definitive) surgical procedure. Only 1 patient mortality was reported at 90 days; the cause of death was unknown. Three patients (2.5%) were reported as alive but lost to follow-up at 90 days from surgery; the majority (96.7%) were alive at 90 days from surgery.

Discussion

In this analysis of NCDB data, we found that 100% were alive at 30 days and >99% were alive at 90 days following surgical resection. This concurs with our hypothesis that pediatric urothelial cancer outcomes are particularly favorable in the short term.

The paucity of available data pertaining to pediatric bladder cancer makes it challenging to guide patients and their families through important decisions regarding their care. To further shed light on this subject, we turned to the NCDB to look at objective, deidentified information for patients between 0-18 years of age. We excluded patients with rhabdomyosarcoma as the management and outcomes for these tumors are well-established.

The goal of this paper is to illuminate the lack of strong data to guide pediatric urologic practice as it pertains to children with urothelial neoplasms originating in the bladder. Adult guidelines currently recommend surveillance cystoscopy for low-risk disease at 3 months and 12 months from initial diagnosis/resection for PUNLMP (8). This would then be followed with annual cystoscopy for at least 5 years which, in a pediatric population, necessitates multiple trips to the operating room, exposing patient to general anesthesia in addition to the emotional and physical toll associated with surgery (9). Although the recurrence rate for PUNLMP following resection is significant (25–47%) in adults, recurrence is reported less frequently in children and is not associated with concurrent invasive carcinoma. Overall prognosis is excellent in both children and adults.

While prognosis is generally excellent, there are pediatric populations at increased risk of urothelial neoplasms as those with certain gene alterations (e.g., p16/lnk4 deletion,

CK 20, and overexpression of p53) and predisposing genetic syndromes (e.g., Costello syndrome, hereditary non-polyposis colorectal cancer syndrome, etc.) (6,10,11). This information, while important, is not yet captured in the NCDB. Various environmental factors including smoking and workplace exposures which are known risk factors for the development bladder tumors in adults (12) but have not been shown to be specifically linked to pediatric urothelial neoplasms. These potential exposures may play a role in the development of pediatric urothelial bladder tumors and remain to be captured and explored in future studies.

The intervention data in NCDB can be challenging to interpret, as it is based on codes with preset descriptors. For example, for the patient noted to have undergone "surgical exploration only" without biopsy or treatment, it is impossible to know whether this meant cystoscopy, open surgery or some other intervention. Similarly, in the 13 patients who underwent a primary biopsy described as "incisional, needle or aspiration", it is unclear whether this represents an initial resection, urine cytology, or some other intervention. NCDB data related to surgical treatment is entered under various subsections as well with preset descriptors rather than CPT or ICD10 procedure codes. While most patients must have undergone at least an endoscopic biopsy in order to establish a tissue diagnosis, the information on surgery type is missing in almost half (63 of 140 patients). In those patients with available data, the registry input is coded as "endoscopic or laparoscopic" without space for elaboration; as such we must infer these patients likely underwent cystoscopic resection. Similarly, 117 patients are noted to have undergone a surgical procedure on the same day of initial diagnosis and 109 patients are categorized as having undergone definitive surgery at the time of diagnosis, which would indicate a biopsy or bladder tumor resection. The challenge in interpreting this intervention data is that many of these entry categories are incomplete or inconsistent, and in addition they do not have CPT codes to further detail the diagnostic/surgical procedures performed. Further, urothelial tumors are not distinguished between low-grade or high-grade as is common in adults, which makes generalizability challenging.

Despite these shortcomings, these data indicate an overall positive short-term prognosis for this pediatric patient cohort, with >99% 90-day survival and largely favorable, non-invasive pathology. This is consistent with data from low-grade papillary urothelial tumors in adult populations (8). Rezaee *et al.* report a 10.7% rate of disease recurrence or death within a 32 month follow up period (2), and this cross-sectional analysis of the NCDB database concurs with their generally favorable short-term outcomes. Unfortunately, we are unable to assess the follow up strategies or surveillance schedules offered to the patients with the NCDB data. Additionally, we are unable to account for specific comorbid conditions of these patients outside the designated Charlson-Deyo mapping table (7). That said, given the largely reassuring observed data, it would be reasonable to question whether these otherwise healthy patients are being overtreated (or at least are subject to overly burdensome surveillance). The current adult NCCN guidelines for low-risk, non-muscle invasive bladder pathology rely heavily on cystoscopic surveillance; unlike in adults, however, in children cystoscopy typically requires general anesthesia. As such, the cost and family burden may be significantly higher among children and adolescents. This is not to say that a role for repeat cystoscopy or surgical intervention—if warranted based on the patient's clinical presentation—should be deferred but rather to emphasize the shortcomings in applying these guidelines to pediatric populations without thorough consideration of the risk/benefits.

Unfortunately, the dearth of longitudinal or qualitative data for this cohort makes it difficult for clinicians to develop an optimized strategy for surveillance of these pediatric patients following initial resection. At present, there is no data-driven, well-defined follow-up guideline for this patient population. A retrospective study analyzing perioperative and long-term follow-up data of nine children who presented with urothelial bladder neoplasms between 2000–2021 was generally consistent with a good prognosis and infrequent recurrences (13).

These findings should be considered within the context of study limitations. Perhaps most notably, we were unable to perform formal hypothesis testing as planned due to too few events (only 1 mortality and no delayed resections within the NCDB follow-up window). To improve generalizability to our cohort and limit errors in coding we excluded patients with rhabdomyosarcoma of the bladder or outcome variables with incomplete data which inevitably affects the power of the study. As the database is poised to capture malignant diagnoses, there is the possibility that PUNLMP cases are underreported given their histopathologic categorization. Nevertheless, NCDB data is limited due to its heavy bias towards metropolitan/urban cancer centers; further, NCDB lacks information on important clinical parameters including

cause of death, disease recurrence greater than 90 days from initial treatment, adjuvant intravesical/systemic therapies or subsequent invasive or non-invasive interventions related to pediatric bladder cancer. This includes information regarding disease progression or recurrence which precludes us from determining event free survival or overall survival beyond 90-day time point. NCDB does provide pathologic and staging data, which allows for a more in depth look at short term outcomes compared to other cancer databases. Furthermore, the relatively large patient cohort given the rarity of this disease offers a unique insight. While limited, the data available through NCDB expounds on the need for a closer look at the long-term outcomes in pediatric urothelial cancer patients and hints at the need for a unique surveillance protocol separate from that of the adult counterpart. These findings serve to guide clinicians in their future discussions with patients regarding invasive monitoring for low grade urothelial carcinoma of the bladder, particularly in short term scenarios.

Conclusions

Among children with urothelial bladder tumors captured in NCDB, we noted excellent short-term survival. This raises the question about whether applying adult protocols to children with low-risk, non-invasive bladder cancer is truly appropriate; in particular, the need for cystoscopic surveillance, which in children requires general anesthesia, may not be fully needed. Future investigations should focus on a more in-depth analysis of disease recurrence and long-term survival outcomes before clinical practice can be confidently changed, however.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-419/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-419/coif). J.C.R. participated in a May 2023 Advisory Board Meeting for Abbvie and served on a DSMB for Xenon/ICON. Neither of these activities in any way overlaps with the content of this manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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